## REMARKS/ARGUMENTS

The foregoing amendments in the specification and claims fully supported by the specification and claims as originally filed, and do not add new matter.

Prior to the present amendment, claims 58-70 were pending in this application. With this amendment, Claims 66-67 have been canceled without prejudice, Claims 58-65 and 69 have been amended to further clarify what applicants have always regarded as their invention, and new Claims 71-75 have been added. Support for the amendments to Claims 58-62 is found in the specification at, for example, page 351, lines 18-32, wherein the protocol and results of the chondrocyte re-differentiation assay are described. Support for newly added Claims 71-75 is found in the specification at, for example, page 347, lines 15-26, wherein the protocol and results for the proliferation of rat utricular supporting cells assay is described. Support for polypeptides comprising polypeptide variants is found in the specification at, for example, page 108, line 38, to page 109, line 26.

Claims 58-65 and 68-75 are pending after entry of the instant amendment. Applicants expressly reserve the right to pursue any canceled matter in subsequent continuation, divisional or continuation-in-part applications.

### I. Priority

Applicants thank the Examiner for granting the priority date of the instant application as March 8, 1999.

### II. Specification

As requested by the PTO, Applicants have reviewed the application and deleted all references to embedded hyperlinks and/or browser-executable code. Further, the ATCC address on page 372, line 34, has been amended and the paragraph beginning at page 374, line 32, has been amended to comply with the provisions of the Budapest Treaty.

### III. Information Disclosure Statement

In response to the Examiner's assertion that the BLAST results cited in the Information Disclosure Statement submitted on May 6, 2002 are not true publications with a publication date, Applicants file herewith, an Information Disclosure Statement listing each reference of the "Blast Search" separately and including authors/inventors, relevant accession numbers and

publication dates. Applicants respectfully request that the listed information be considered by the Examiner and be made of record in the above-identified application.

## IV. Claim Rejections Under 35 U.S.C. § 112, Second Paragraph

Claims 58-63, 66-67 and 69-70 are rejected under 35 U.S.C. § 112, second paragraph, as allegedly "being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention." In particular, the Examiner asserts that the limitations that the claimed protein comprises an "extracellular domain" or an "extracellular domain ... lacking its associated signal sequence" are indefinite.

Without acquiescing to the Examiner's position, and solely in the interest of expediting prosecution in this case, Applicants submit that Claims 58-63, as amended herein, as well as dependent Claims 69-70, no longer recite an extracellular domain of a polypeptide or an extracellular domain of a polypeptide lacking its associated signal peptide. Applicants further submit that the cancellation of Claims 66-67 renders the rejection of these claims moot.

The Examiner further asserts that Claim 70 is indefinite for reciting "epitope tag" because allegedly "the exact meaning of the phrase is not clear." (Page 3 of the instant Office Action).

Applicants respectfully submit that the term "epitope tagged" is defined in the specification at page 130, lines 14-20:

> The term "epitope tagged" when used herein refers to a chimeric polypeptide comprising a PRO polypeptide fused to a "tag polypeptide". The tag polypeptide has enough residues to provide an epitope against which an antibody can be made, yet is short enough such that it does not interfere with activity of the polypeptide to which it is fused. The tag polypeptide preferably also is fairly unique so that the antibody does not substantially cross-react with other epitopes. Suitable tag polypeptides generally have at least six amino acid residues and usually between about 8 and 50 amino acid residues (preferably, between about 10 and 20 amino acid residues).

Examples of epitope tags are disclosed in the specification at page 184, lines 14-27. Based upon the disclosure in the specification as filed, one of ordinary skill in the art would understand that an "epitope tag" is a tag that allows for purification by binding to a specific antibody.

Accordingly, Applicants request that the rejection of Claims 58-63, 66-67 and 69-70 under 35 U.S.C. §112, second paragraph, be withdrawn.

## V. Claim Rejections Under 35 U.S.C. §112, First Paragraph (Written Description)

Claims 58-62 and 69-70 are rejected under 35 U.S.C. §112, first paragraph, as allegedly lacking adequate written description. The Examiner asserts that "the claims are drawn to a genus of polypeptides that are defined only by sequence identity and may have very different structures and functions." (Page 4 of the instant Office Action).

Without acquiescing to the Examiner's position, Applicants submit that Claims 58-62, as amended herein, recite polypeptides having at least 80% amino acid sequence identity to the polypeptide of SEQ ID NO:523, wherein said polypeptide induces chondrocyte re-differentiation. Newly added Claims 71-75 recite polypeptides having at least 80% amino acid sequence identity to the polypeptide of SEQ ID NO:523, wherein said polypeptide induces proliferation of rat utricular supporting cells.

Example 126 of the present application (page 351, lines 18-32) provides the protocol for the chondrocyte re-differentiation assay. By following the disclosure in the specification, one skilled in the art can easily test whether a variant PRO337 polypeptide induces chondrocyte re-differentiation. Example 116 of the present application (page 347, lines 15-26) provides the protocol for the proliferation of rat utricular supporting cells assay. By following the disclosure in the specification, one skilled in the art can easily test whether a variant PRO337 polypeptide induces proliferation of rat utricular supporting cells.

The specification further describes methods for the determination of percent identity between two amino acid sequences (See pages 122, line 34 to page 125, line 37). In fact, the specification teaches specific parameters to be associated with the term "percent identity" as applied to the present invention. The specification further provides detailed guidance as to changes that may be made to a PRO polypeptide without adversely affecting its activity (page 180, line 10, to page 183, line 8). This guidance includes a listing of exemplary and preferred substitutions for each of the twenty naturally occurring amino acids (Table 6, page 182). Accordingly, one of skill in the art could identify whether a variant PRO337 sequence falls within the parameters of the claimed invention. Once such an amino acid sequence is identified, the specification sets forth methods for making the amino acid sequences (see page 180, line 9 to page 184, line 35) and methods of preparing the PRO polypeptides (see page 185, line 36 and onward).

As noted by the Examiner, factors to be considered in evidencing possession of a claimed genus include "disclosure of complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof. (Page 4 of the Office Action mailed June 20, 2005). As discussed above, Applicants have recited structural features, namely, 80% sequence identity to the polypeptide of SEQ ID NO:523, which are common to the genus. Applicants have also provided guidance as to how to make the recited variants of SEQ ID NO:523, including listings of exemplary and preferred sequence substitutions. The genus of claimed polypeptides is further defined by having a specific functional activity, either ability to induce chondrocyte re-differentiation, or ability to induce proliferation of rat utricular supporting cells. Accordingly, a description of the claimed genus has been achieved.

Therefore, withdrawal of the written description rejection of Claims 58-62 and 68-70 under 35 U.S.C. §112, first paragraph, is respectfully requested.

## VI. Claim Rejections Under 35 U.S.C. §112, First Paragraph (Deposit Requirement)

Claims 58-63 and 68-70 are rejected under 35 U.S.C. §112, first paragraph, as allegedly "failing to provide an adequate written description of the invention and failing to provide an enabling disclosure without complete evidence either that the claimed biological materials are known and readily available to the public or complete evidence of the deposit of the biological materials." (Page 6 of the instant Office Action).

Without acquiescing to the Examiner's rejection, the paragraph beginning at page 374, line 32, has been amended to state,

> These deposit were made under the provisions of the Budapest Treaty on the International Recognition of the Deposit of Microorganisms for the Purpose of Patent Procedure and the Regulations there under (Budapest Treaty). This assures maintenance of a viable culture of the deposit for 30 years from the date of deposit and for at least five (5) years after the most recent request for the furnishing of a sample of the deposit received by the depository. The deposits will be made available by ATCC under the terms of the Budapest Treaty, and subject to an agreement between Genentech, Inc. and ATCC, which assures that all restrictions imposed by the depositor on the availability to the public of the deposited material will be irrevocably removed upon the granting of the pertinent U.S. patent, assures permanent and unrestricted availability of the progeny of the culture of the deposit to the public upon issuance of the pertinent U.S. patent or upon laying open to the public of any U.S. or foreign patent application,

whichever comes first, and assures availability of the progeny to one determined by the U.S. Commissioner of Patents and Trademarks to be entitled thereto according to 35 U.S.C. § 122 and the Commissioner's rules pursuant thereto (including 37 C.F.R. § 1.14 with particular reference to 886 OG 638).

Accordingly, Applicants believe that all of the requirements of 37 C.F.R. §§ 1.801-1.809 are met, and the Examiner is respectfully requested to reconsider and withdraw the rejection of Claims 58-63 and 68-70 under 35 U.S.C. §112, first paragraph.

## VII. Claim Rejections Under 35 U.S.C. §112, First Paragraph (Scope of Enablement)

Claims 58-62 and 69-70 are rejected under 35 U.S.C. §112, first paragraph, allegedly "because the specification, were it enabling for an isolated polypeptide comprising SEQ ID NO:523, would still not provide enablement for polypeptides having at least 80% amino acid sequence identity to SEQ ID NO:523." (Page 8 of the instant Office Action).

The Examiner acknowledges that "Applicants have taught the polypeptide of SEQ ID NO:523, as well as the putative signal sequence." The Examiner asserts, however, that "Applicants have not asserted any activity for polypeptides comprising SEQ ID NO:523" and that "polypeptide variants could have structures and functions that are very different from the polypeptide of SEQ ID NO:523." The Examiner concludes that "because there is no activity disclosed for the PRO337 polypeptide, there would be no means for predicting or identifying other polypeptides that would have a similar activity" (Page 9 of the instant Office Action).

Applicants respectfully submit that the instant specification discloses that PRO337 tested positive in the chondrocyte re-differentiation assay, and therefore can be used in the treatment of various bone and/or cartilage disorders such as, for example, sports injuries and arthritis (see Example 126). The specification further discloses that PRO337 tested positive in the proliferation of rat utricular supporting cells assay, and therefore can be used to induce the regeneration of auditory hair cells and for treating hearing loss in mammals (see Example 116). Thus the specification discloses at least two specific activities for the PRO337 polypeptide, and based upon this disclosure, one of ordinary skill in the art would understand how to use the PRO337 polypeptide.

The skilled artisan would therefore also understand how to use variants of PRO337 that had the same activity. Without acquiescing to the Examiner's position, Applicants submit that Claims 58-62, as amended herein, recite polypeptides having at least 80% amino acid sequence

identity to SEQ ID NO:523, wherein said polypeptide induces chondrocyte re-differentiation. Newly added Claims 71-75 recite polypeptides having at least 80% amino acid sequence identity to SEQ ID NO:523, wherein said polypeptide induces proliferation of rat utricular supporting cells.

Example 126 of the present application (page 351, lines 18-32) provides the protocol for the chondrocyte re-differentiation assay. By following the disclosure in the specification, one skilled in the art can easily test whether a variant PRO337 polypeptide induces chondrocyte re-differentiation. Example 116 of the present application (page 347, lines 15-26) provides the protocol for the proliferation of rat utricular supporting cells assay. By following the disclosure in the specification, one skilled in the art can easily test whether a variant PRO337 polypeptide induces proliferation of rat utricular supporting cells.

The specification further describes methods for the determination of percent identity between two amino acid sequences (See pages 122, line 34 to page 125, line 37). In fact, the specification teaches specific parameters to be associated with the term "percent identity" as applied to the present invention. The specification further provides detailed guidance as to changes that may be made to a PRO polypeptide without adversely affecting its activity (page 180, line 10, to page 183, line 8). This guidance includes a listing of exemplary and preferred substitutions for each of the twenty naturally occurring amino acids (Table 6, page 182). Accordingly, one of skill in the art could identify whether a variant PRO337 sequence falls within the parameters of the claimed invention. Once such an amino acid sequence is identified, the specification sets forth methods for making the amino acid sequences (see page 180, line 9 to page 184, line 35) and methods of preparing the PRO polypeptides (see page 185, line 36 and onward).

Therefore, Applicants respectfully submit that the specification provides ample guidance such that one of skill in the art could readily test a variant polypeptide to determine whether it induces chondrocyte re-differentiation or induces proliferation of rat utricular supporting cells by the methods set forth in Example 126 and Example 116. Furthermore, one of ordinary skill in the art has a sufficiently high level of technical competence to identify sequences with at least 80% identity to SEQ ID NO:523. Accordingly, one of ordinary skill could practice the claimed invention without undue experimentation.

The claims currently recite polypeptide sequences associated with one of two specific biological activities. These biological activities together with the well defined relatively high degree of sequence identity and general knowledge in the art at the time the invention was made, sufficiently defines the claimed genus such that, one skilled in the art, at the effective date of the present application, would have known how to make and use the claimed polypeptide sequences without undue experimentation. As the M.P.E.P. states, "[t]he fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation."[1]

As discussed above, a considerable amount of experimentation is permissible, if it is merely routine. Applicants submit that the identification of variant PRO337 polypeptides having at least 80% identity to SEQ ID NO:523, wherein said polypeptide is induces chondrocyte re-differentiation, or induces proliferation of rat utricular supporting cells, can be performed by techniques that were well known in the art at the priority date of this application, and that the performance of such work does not require undue experimentation.

Accordingly, withdrawal of the enablement rejection of Claims 58-62 and 68-70 under 35 U.S.C. §112, first paragraph, is respectfully requested.

## VIII. Claim Rejections Under 35 U.S.C. §102

Claims 58-61 are rejected under 35 U.S.C. §102(b) as allegedly being anticipated by Struyk *et al.* (The Journal of Neuroscience, 15(3):2141-2156, March 1995). Struyk *et al.* teach an isolated polypeptide having 91% amino acid sequence identity with SEQ ID NO:523, and having 97% amino acid sequence identity with the polypeptide of SEQ ID NO:523 lacking its associated signal peptide.

Applicants respectfully submit that a rejection under 35 U.S.C. § 102 can only be proper if the cited reference recites every element of the rejected claim. "For a prior art reference to anticipate in terms of 35 U.S.C. §102, *every* element of the claimed invention must be shown in a single reference." See *In re Bond*, 910 F.2d 831, 15 U.S.P.Q.2d 1566 (Fed. Cir. 1990). M.P.E.P. §2131 further provides, "A claim is anticipated only if *each* and *every* element as set forth in the

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[1] M.P.E.P. §2164.01 citing *In re Certain Limited-charge Cell Culture Microcarriers,* 221 U.S.P.Q. 1165, 1174 (Int'l Trade Comm'n 1983), *aff' sub nom. Massachusetts Institute of Technology v. A.B. Fortia*, 774 F.2d 1104, 227 U.S.P.Q. 428 (Fed. Cir. 1985).

claim is found, either expressly or inherently described in a single prior art reference.' *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 U.S.P.Q.2d 1051, 1053 (Fed. Cir. 1987). 'The identical invention must be shown in as complete detail as contained in the ... claim.' *Richardson v. Suzuki Motor Co.*, 868 F.2d 1226, 1236, 9 U.S.P.Q.2d 1913, 1920 (Fed. Cir. 1989)."

Without acquiescing to the Examiner's position, Applicants submit that Claims 58-61, as amended herein, recite polypeptides having at least 80% amino acid sequence identity to SEQ ID NO:523, wherein said polypeptide induces chondrocyte re-differentiation. Newly added Claims 71-75 recite polypeptides having at least 80% amino acid sequence identity to SEQ ID NO:523, wherein said polypeptide induces proliferation of rat utricular supporting cells.

The polypeptide of Struyk *et al.*, termed "neurotrimin," does not have the recited function of inducing chondrocyte re-differentiation or of inducing proliferation of rat utricular supporting cells. In fact, Struyk *et al.* discloses that expression of neurotrimin is "only detectable in the adult nervous system and not in a wide variety of non-neural tissues examined" (page 2148, col. 2). Neurotrimin expression is further restricted to postmitotic neurons, and it appears to have a specific function in generating diversity of the neuronal cell surface during development (page 2152, col. 2). Given that the neurotrimin polypeptide of Struyk *et al.* is not even expressed in other cell types such as chondrocytes or rat utricular supporting cells, it is highly improbable that it induces chondrocyte re-differentiation or induces proliferation of rat utricular supporting cells, as recited in the claims. Therefore the polypeptide of Struyk *et al.* does not anticipate the claims.

Accordingly, withdrawal of the rejection of Claims 58-61 under 35 U.S.C. §102(b) as anticipated by Struyk *et al.* is respectfully requested.

## IX. Claim Rejections Under 35 U.S.C. §103

Claims 58-61 and 69-70 are rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over Struyk *et al.* in view of Grose (U.S. Patent No. 5,710,248, issued January 20, 1998). Struyk *et al.* teach an isolated polypeptide having 91% amino acid sequence identity with SEQ ID NO:523, and having 97% amino acid sequence identity with the polypeptide of SEQ ID NO:523 lacking its associated signal peptide. Grose teaches a peptide tag for immunopurification and immunoprecipitation.

As discussed above, Struyk *et al.* does not disclose each and every limitation of Claim 58, or those claims dependent upon Claim 58, because Struyk *et al.* does not disclose a polypeptide that induces chondrocyte re-differentiation or induces proliferation of rat utricular supporting cells, as recited in the claims. Grose does not cure the deficiencies of Struyk *et al.*, as the teachings of Grose are limited to polypeptide tags. Thus Applicants respectfully submit that the instant claims are not obvious over Struyk *et al.* in view of Grose.

Accordingly, withdrawal of the rejection of Claims 58-61 and 69-70 under 35 U.S.C. §103(a) over Struyk *et al.* in view of Grose is respectfully requested.

## CONCLUSION

In conclusion, the present application is believed to be in *prima facie* condition for allowance, and an early action to that effect is respectfully solicited. Should there be any further issues outstanding, the Examiner is invited to contact the undersigned attorney at the telephone number shown below.

Please charge any additional fees, including fees for additional extension of time, or credit overpayment to Deposit Account No. **08-1641** (referencing Attorney's Docket No. **39780-2630 P1C12**).

Respectfully submitted,

Date: September 13, 2005

By: _____
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